

Supplementary Online Content

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eReference.

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. World Health Organization defined daily doses for antiseizure medications used in this study¹

Antiseizure Medication	Defined Daily Dose (mg)
First-generation	
Carbamazepine	1000
Phenytoin	300
Valproate	1500
Second-generation	
Acetazolamide	750
Clobazam	20
Eslicarbazepine acetate	800
Felbamate	2400
Gabapentin	1800
Lacosamide	300
Levetiracetam	1500
Lamotrigine	300
Oxcarbazepine	1000
Perampanel	8
Pregabalin	300
Rufinamide	1400
Retigabine	900
Remacemide	N/A [^]
Tiagabine	30
Topiramate	300
Vigabatrin	2000
Zonisamide	200
[^] Defined daily dose of remacemide was not available.	

eTable 2. Generations of antiseizure medications prescribed in the three epochs

ASM Type	1 July 1982 to 30 June 1992		1 July 1992 to 30 June 2002		1 July 2002 to 30 April 2016		Total
First ASM regimen - n (%)							
<i>First-generation</i>	115	(77.7)	415	(58.6)	294	(31.3)	824
<i>Second-generation</i>	33	(22.3)	293	(41.4)	645	(68.7)	971
Subsequent ASM regimens - n (%)							
Monotherapy - n (%)	27	(90.0)	213	(51.6)	311	(31.0)	551
<i>First-generation</i>	26	(96.3)	129	(60.6)	91	(29.3)	246
<i>Second-generation</i>	1	(3.70)	84	(39.4)	220	(70.7)	305
Combination therapy - n (%)	3	(10.0)	200	(48.4)	692	(69.0)	895
<i>First-generation only</i>	0	(0)	8	(4.00)	3	(0.43)	11
<i>Second-generation only</i>	3	(100)	174	(87.0)	569	(82.2)	746
<i>First-generation and Second- generation</i>	0	(0)	18	(9.00)	120	(17.3)	138
Total number of ASM regimens	178		1,121		1,942		3,241
ASM, antiseizure medication							

eTable 3. Summary of intolerable adverse effects related to discontinuation of antiseizure medications according to MedDRA classifications

Adverse effect [^]	n (% of withdrawals)	
Nervous system disorders	178	(35.3)
Psychiatric disorders	117	(23.2)
General disorders and administration site conditions	116	(23.0)
Skin and subcutaneous tissue disorders	107	(21.2)
Gastrointestinal disorders	82	(16.3)
Weight gain or loss ¹	33	(6.55)
Metabolism and nutrition disorders	20	(3.97)
Reproductive system and breast disorders	5	(0.99)
Cardiac disorders	2	(0.40)
Eye disorders	2	(0.40)
Musculoskeletal and connective tissue disorders	2	(0.40)
Respiratory, thoracic and mediastinal disorders	2	(0.40)
Blood and lymphatic system disorders	1	(0.20)
Endocrine disorders	1	(0.20)
Hepatobiliary disorders	1	(0.20)
Injury, poisoning and procedural complications	1	(0.20)
Renal and urinary disorders	1	(0.20)
Vascular disorders	1	(0.20)
Total	504	(100)
[^] Patient could experience multiple adverse effects leading to single drug withdrawal.		
1. Weight gain and weight loss are coded as "Investigations" in MedDRA.		
MedDRA, Medical Dictionary for Regulatory Activities.		

eTable 4. Univariable screening of potential risk factors for developing intolerable adverse effects to antiseizure medication therapy

Potential Risk Factors	Intolerable Adverse Effect Rates^ (%)	Hazard Ratio	95% Confidence Interval	p-value
Age at starting the ASM, years				
18-64 vs. <18	416/2593 (16.0) vs. 35/354 (9.89)	1.61	(1.12-2.33)	0.010
≥65 vs. <18	53/294 (18.0) vs. 35/354 (9.89)	1.96	(1.26-3.06)	0.003
≥65 vs. 18-64	53/294 (18.0) vs. 416/2593 (16.0)	1.22	(0.91-1.63)	0.189
Sex (Male vs. Female)	206/1690 (19.2) vs. 298/1551 (12.2)	0.60	(0.50-0.73)	<0.001
Epilepsy type (Focal vs. Generalised)	419/2575 (16.3) vs. 85/666 (12.8)	1.28	(0.99-1.64)	0.055
Duration of epilepsy, continuous		1.00	(1.00-1.00)	0.28
Pretreatment seizure number (>5 vs. ≤5)	285/1633 (17.5) vs. 85/1608 (13.6)	1.29	(1.06-1.56)	0.012
History of drug abuse (Yes vs. No)	67/389 (17.2) vs. 437/2852 (15.3)	1.11	(0.84-1.45)	0.47
History of alcohol abuse (Yes vs. No)	97/687 (14.1) vs. 407/2554 (15.9)	0.84	(0.66-1.07)	0.17
History of psychiatric disorders (Yes vs. No)	174/1019 (17.1) vs. 330/2222 (14.9)	1.12	(0.90-1.38)	0.30
History of learning disability (Yes vs. No)	16/113 (14.2) vs. 488/3128 (15.6)	1.01	(0.59-1.73)	0.97
Number of concomitant ASMs, continuous		1.19	(0.96-1.48)	0.11
Number of previous intolerable adverse effects, continuous		1.25	(1.17-1.34)	<0.001
Number of previous ASM failed due to poor seizure control, continuous		0.89	(0.69-1.16)	0.39
ASM type (Second-generation vs. First-generation)	342/2064 (16.6) vs. 162/1177 (13.8)	1.16	(0.94-1.41)	0.16
^ Intolerable adverse effect rates of ASM regimens in comparison groups.				
ASM, antiseizure medication				

eTable 5. Individual antiseizure medication prescribed as the initial monotherapy in the three epochs

Antiseizure Medication	1 July 1982 to 30 June 1992		1 July 1992 to 30 June 2002		1 July 2002 to 30 April 2016	
First-generation - n (%)	115	(77.7)	415	(58.6)	294	(31.3)
<i>Carbamazepine</i>	82	(55.4)	198	(28.0)	43	(4.58)
<i>Phenytoin</i>	10	(6.76)	1	(0.14)	1	(0.11)
<i>Valproate</i>	23	(15.5)	216	(30.5)	250	(26.6)
Second-generation - n (%)	33	(22.3)	293	(41.4)	645	(68.7)
<i>Eslicarbazepine acetate</i>	0	(0)	0	(0)	3	(0.32)
<i>Felbamate</i>	0	(0)	8	(1.13)	0	(0)
<i>Gabapentin</i>	0	(0)	27	(3.81)	0	(0)
<i>Lacosamide</i>	0	(0)	0	(0)	1	(0.11)
<i>Levetiracetam</i>	0	(0)	0	(0)	215	(22.9)
<i>Lamotrigine</i>	31	(20.9)	213	(30.1)	307	(32.7)
<i>Oxcarbazepine</i>	2	(1.35)	16	(2.26)	56	(5.96)
<i>Pregabalin</i>	0	(0)	0	(0)	2	(0.21)
<i>Remacemide</i>	0	(0)	3	(0.42)	0	(0)
<i>Tiagabine</i>	0	(0)	24	(3.39)	0	(0)
<i>Topiramate</i>	0	(0)	2	(0.28)	61	(6.50)
Total - n (%)	148	(100)	708	(100)	939	(100)

eTable 6. Multivariable analysis[^] of adverse effects leading to discontinuation of the initial antiseizure medication monotherapy commenced in the three epochs, stratified by antiseizure medication generation

	1 July 1982 to 30 June 1992 vs. 1 July 1992 to 30 June 2002			1 July 1982 to 30 June 1992 vs. 1 July 2002 to 30 April 2016			1 July 1992 to 30 June 2002 vs. 1 July 2002 to 30 April 2016		
ASM Generation	aHR	(95% CI)	<i>p</i> -value	aHR	(95% CI)	<i>p</i> -value	aHR	(95% CI)	<i>p</i> -value
First-generation	0.63	(0.33-1.20)	0.16	0.73	(0.36-1.49)	0.39	1.16	(0.75-1.80)	0.51
Second-generation	0.69	(0.21-2.28)	0.55	0.57	(0.18-1.84)	0.35	0.83	(0.57-1.21)	0.32
[^] Cox regression with adjustment of age at start of treatment, sex, and pretreatment seizure number.									
aHR, adjusted hazard ration after adjustment of age at start of treatment, sex, and pretreatment seizure number; ASM, antiseizure medication; CI, confidence interval									

eTable 7. Pairwise comparison of adverse effects leading to discontinuation of the initial antiseizure medication monotherapy commenced in the three epochs

	1 July 1982 to 30 June 1992 vs. 1 July 1992 to 30 June 2002		1 July 1982 to 30 June 1992 vs. 1 July 2002 to 30 April 2016		1 July 1992 to 30 June 2002 vs. 1 July 2002 to 30 April 2016	
Adverse effect [^]	<i>p</i> -value	corrected <i>p</i> -value	<i>p</i> -value	corrected <i>p</i> -value	<i>p</i> -value	corrected <i>p</i> -value
Nervous system disorders	0.013	0.039	0.022	0.044	0.56	0.56
Psychiatric disorders	0.23	0.23	0.007	0.013	0.002	0.006
Skin and subcutaneous tissue disorders	0.058	0.12	0.035	0.11	0.90	0.90
Gastrointestinal disorders	0.10	0.20	0.71	0.71	0.016	0.048
[^] Adverse effects with <i>p</i> -value<0.10 in the three epochs comparisons were included for pairwise comparison.						

eTable 8. Pairwise comparison of crude rates of intolerable adverse effects between individual antiseizure medications used as the initial monotherapy[^]

ASM	Crude Intolerable AE rates	<i>p</i> -value	corrected <i>p</i> -value
OXC vs VPA	16/74 (21.6%) vs. 55/489 (11.3%)	0.005	0.075
LTG vs OXC	64/551 (11.6%) vs. 16/74 (21.6%)	0.010	0.14
TPM vs VPA	13/63 (20.6%) vs. 55/489 (11.3%)	0.052	0.68
LTG vs TPM	64/551 (11.6%) vs. 13/63 (20.6%)	0.070	0.84
CBZ vs VPA	48/323 (14.9%) vs. 55/489 (11.3%)	0.083	0.91
LEV vs OXC	31/215 (14.4%) vs. 16/74 (21.6%)	0.095	0.95
CBZ vs OXC	48/323 (14.9%) vs. 16/74 (21.6%)	0.13	>0.99
CBZ vs LTG	48/323 (14.9%) vs. 64/551 (11.6%)	0.14	>0.99
LEV vs VPA	31/215 (14.4%) vs. 55/489 (11.3%)	0.23	>0.99
LEV vs TPM	31/215 (14.4%) vs. 13/63 (20.6%)	0.32	>0.99
LEV vs LTG	31/215 (14.4%) vs. 64/551 (11.6%)	0.32	>0.99
CBZ vs TPM	48/323 (14.9%) vs. 13/63 (20.6%)	0.41	>0.99
OXC vs TPM	16/74 (21.6%) vs. 13/63 (20.6%)	0.62	>0.99
CBZ vs LEV	48/323 (14.9%) vs. 31/215 (14.4%)	0.77	>0.99
LTG vs VPA	64/551 (11.6%) vs. 55/489 (11.3%)	0.78	0.78
^ ASMs prescribed to more than 50 patients as the initial monotherapy were included, n=1,715; LTG, n=551; VPA, n=489; CBZ, n=323; LEV, n=215; OXC, n=74; and TPM, n=63.			
AE, adverse effect; ASM, antiseizure medication; CBZ, carbamazepine; LEV, levetiracetam; LTG, lamotrigine, OXC, oxcarbazepine; TPM, topiramate; VPA, valproate.			

eTable 9. Subdistribution hazard ratios of withdrawal due to various adverse events reported in at least 50 patients between individual antiseizure medications used as the initial monotherapy[^]

(a) nervous system disorder			
ASM	Subdistribution Hazard Ratio*	(95% Confidence Interval)	p-value[#]
OXC vs. CBZ	2.13	(0.82-5.55)	0.12
OXC vs. LEV	1.32	(0.51-3.42)	0.57
OXC vs. LTG	4.00	(1.55-10.3)	0.004
OXC vs. TPM	0.62	(0.22-1.73)	0.36
OXC vs. VPA	1.80	(0.73-4.46)	0.20
TPM vs. CBZ	3.45	(1.42-8.40)	0.006
TPM vs. LEV	2.14	(0.87-5.24)	0.096
TPM vs. LTG	6.48	(2.70-15.5)	<0.001
TPM vs. VPA	2.92	(1.28-6.62)	0.011
LTG vs. CBZ	0.53	(0.25-1.16)	0.11
LTG vs. LEV	0.33	(0.15-0.71)	0.004
LTG vs. VPA	0.45	(0.22-0.92)	0.029
LEV vs. CBZ	1.61	(0.73-3.59)	0.24
LEV vs. VPA	1.36	(0.64-2.90)	0.42
CBZ vs. VPA	0.84	(0.41-1.74)	0.65

(b) skin and subcutaneous tissue disorders[†]			
ASM	Subdistribution Hazard Ratio*	(95% Confidence Interval)	p-value[#]
OXC vs. CBZ	0.87	(0.34-2.27)	0.78
OXC vs. LEV	22.4	(2.57-194)	0.005
OXC vs. LTG	1.47	(0.55-3.91)	0.44
OXC vs. VPA	6.96	(2.06-23.5)	0.002
LTG vs. CBZ	0.6	(0.36-0.98)	0.041
LTG vs. LEV	15.2	(2.11-110)	0.007
LTG vs. VPA	4.74	(1.81-12.4)	0.002
LEV vs. CBZ	0.04	(0.01-0.29)	0.001
LEV vs. VPA	0.31	(0.04-2.66)	0.29
CBZ vs. VPA	7.97	(3.14-20.2)	<0.001

(c) general disorders and administration site conditions			
ASM	Subdistribution Hazard Ratio*	(95% Confidence Interval)	p-value[#]
OXC vs. CBZ	1.96	(0.51-7.55)	0.33
OXC vs. LEV	0.85	(0.23-3.14)	0.81
OXC vs. LTG	2.46	(0.65-9.28)	0.18
OXC vs. TPM	0.68	(0.15-3.05)	0.61
OXC vs. VPA	1.27	(0.37-4.41)	0.71
TPM vs. CBZ	2.89	(0.84-10.0)	0.093
TPM vs. LEV	1.26	(0.39-4.01)	0.70
TPM vs. LTG	3.64	(1.12-11.9)	0.032
TPM vs. VPA	1.88	(0.61-5.77)	0.27
LTG vs. CBZ	0.80	(0.29-2.18)	0.66
LTG vs. LEV	0.35	(0.15-0.80)	0.013
LTG vs. VPA	0.52	(0.21-1.24)	0.14
LEV vs. CBZ	2.30	(0.86-6.19)	0.098
LEV vs. VPA	1.50	(0.63-3.57)	0.36
CBZ vs. VPA	0.65	(0.26-1.64)	0.36

(d) psychiatric disorders			
ASM	Subdistribution Hazard Ratio*	(95% Confidence Interval)	p-value[#]
OXC vs. CBZ	6.04	(1.36-26.8)	0.018
OXC vs. LEV	0.67	(0.23-1.91)	0.45
OXC vs. LTG	3.91	(1.20-12.7)	0.023
OXC vs. TPM	0.34	(0.11-1.05)	0.061
OXC vs. VPA	5.69	(1.42-22.7)	0.014
TPM vs. CBZ	17.9	(4.73-67.6)	<0.001
TPM vs. LEV	1.97	(0.87-4.50)	0.11
TPM vs. LTG	11.6	(4.39-30.6)	<0.001
TPM vs. VPA	16.8	(5.08-55.9)	<0.001
LTG vs. CBZ	1.54	(0.41-5.76)	0.52
LTG vs. LEV	0.17	(0.07-0.40)	<0.001
LTG vs. VPA	1.45	(0.41-5.12)	0.56
LEV vs. CBZ	9.06	(2.66-30.9)	<0.001
LEV vs. VPA	8.53	(2.69-27.1)	<0.001
CBZ vs. VPA	0.94	(0.20-4.51)	0.94

[^] ASMs prescribed to more than 50 patients as the initial monotherapy were included. LTG, n=551; VPA, n=489; CBZ, n=323; LEV, n=215; OXC, n=74; and TPM, n=63.
[†] TPM was excluded from the analysis of skin and subcutaneous tissue disorders as no patient reported the event.
^{*} After adjustment of age at start of treatment, sex, and pretreatment seizure number.
[#] Multivariable Fine-Gray compete risk regression with adjustments of age at start of treatment, sex, and pretreatment seizure number.
 ASM, antiseizure medication; CBZ, carbamazepine; LEV, levetiracetam; LTG, lamotrigine; OXC, oxcarbazepine; TPM, topiramate; VPA, valproate.

eReference

1. ATC/DDD Index 2019. (Accessed March 19, 2019, at https://www.whooc.no/atc_ddd_index/.)